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Gene-Environment Interplay Between Cannabis and Psychosis

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Cannabis use is considered a contributory cause of schizophrenia and psychotic illness. However, only a small proportion of cannabis users develop psychosis. This can partly be explained by the amount and duration of the consumption of cannabis and by its strength but also by the age at which individuals are first exposed to cannabis. Genetic factors, in particular, are likely to play a role in the short- and the long-term effects cannabis may have on psychosis outcome. This review will therefore consider the interplay between genes and exposure to cannabis in the development of psychotic symptoms and schizophrenia. Studies using genetic, epidemiological, experimental, and observational techniques will be discussed to investigate gene-environment correlation gene-environment interaction, and higher order interactions within the cannabis-psychosis association. Evidence suggests that mechanisms of gene-environment interaction are likely to underlie the association between cannabis and psychosis. In this respect, multiple variations within multiple genes—rather than single genetic polymorphisms—together with other environmental factors (eg, stress) may interact with cannabis to increase the risk of psychosis. Further research on these higher order interactions is needed to better understand the biological pathway by which cannabis use, in some individuals, may cause psychosis in the short- and long term.

Key words: psychotic disorders/genetics/environment/cannabis/tetrahydrocannabinol/schizophrenia

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Introduction

There have been claims for many years that cannabis use can induce a psychotic illness,[1] termed cannabis psychosis by some psychiatrists.[2,3] Recent studies show that the use of cannabis in the general population is associated with increased levels of psychotic symptoms.[4] Furthermore, a number of studies have shown that patients with diagnosed psychosis, use more cannabis than the general population.[5,6] All the above are compatible with the idea that use of cannabis may increase the risk of psychotic illnesses like schizophrenia. In patients with an established psychotic disorder, cannabis use is associated with more and earlier relapses[7] and poorer psychosocial functioning[8] but perhaps surprisingly also with less negative[9,10] and affective symptoms.[11] These latter findings, together with data from studies asking patients to complete self-report questionnaires, identified enhancement of positive affect, social acceptance, and coping with negative affect[12,13] as the main motives for patients to use cannabis. This led to the notion that cannabis use might be secondary to psychosis (or liability to psychosis).

Several meta-analyses on this issue of whether cannabis use is a cause or consequence of psychosis have now been published, consistently showing that use of cannabis (analyzed as lifetime use in most studies and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) cannabis dependence in some) increases the risk to develop later psychotic symptoms or psychotic illness with a factor 2.[14,15] This effect size held regardless of whether only studies using *DSM-IV* diagnoses of psychotic disorder were included or whether, in addition, studies using the broader psychosis phenotype as the outcome measure were also considered. The association between cannabis and subsequent psychosis in these population-based studies cannot be explained entirely by confounding because in these studies the effect of cannabis on psychosis outcome remained significant after adjustment for factors such as age, sex, social class, ethnicity, urbanicity, and use of other drugs. Thus, cannabis use is now widely accepted as a modest contributory cause of schizophrenia and similar illnesses.[16]

However, it is manifestly obvious that only a small proportion of cannabis users develop psychosis. This can partly be explained on the basis of the amount and duration of consumption because there is a dose-response effect.[4,17,18] In addition, some studies suggest that adolescence is a particularly vulnerable period for a person to be exposed to cannabis. In the Dunedin birth cohort, Arseneault et al[19] showed that the onset of cannabis use before the age of 15 years was associated with a greater risk of developing schizophreniform disorder at age 26 years than the onset of cannabis use at an older age. This finding was replicated by Stefanis et al[20] and recently by Konings et al[21], who both investigated the association between age of first cannabis use and lifetime subclinical psychotic symptoms in a general population sample. In this last study, the association between cannabis use and psychosis was studied for the first time in a non-Western society, showing once more that early exposure to cannabis (before the age of 14 years in this sample) was associated with a greater risk to develop psychotic symptoms than first exposure during later adolescence.

Another possible explanation as to why only a minority of individuals develop psychosis is that certain individuals may be especially genetically vulnerable. This review will therefore consider the interplay between genes and exposure to cannabis in the development of psychotic symptoms and schizophrenia. Genetic, epidemiological, observational, and experimental findings will be discussed to investigate mechanisms of both gene-environment interaction (GEI) and gene-environment correlation (rGE) within the cannabis-psychosis association.

Gene-Environment Correlation

Is Cannabis Use Influenced by Genes?

rGE refers to the fact that exposure to an environmental risk factor is not random but is influenced by the individual's genotype. In the case of cannabis and psychosis, genetic predisposition for psychosis would increase the risk to use cannabis and to develop psychosis independently of each other. Thus, in order to determine causality between cannabis use and psychotic illness, rGE needs to be considered. A first step is then to investigate the heritability of cannabis use and abuse. Family studies have shown that cannabis use aggregates in families,[22] which indicates that individual differences in cannabis use may be due to either genetic or common environmental influences, or both. Twin studies examining both monozygotic and dizygotic twins have shown that the degree to which genetic and environmental influences contribute to the variation in cannabis involvement seems to differ across stages of use. Initiation and early patterns of use of cannabis seem to be more strongly influenced by environmental factors but cannabis abuse and dependence more strongly by genetic vulnerability.[23,24] Genetic vulnerability to cannabis abuse seems to be polygenic and may be mediated by early response to cannabis use[25] or personality traits, such as, eg, sensation seeking.[26]

Are the Genetic Influences on Cannabis Use Associated With Psychosis Proneness?

Some have suggested that the association between cannabis and psychosis may be due to the fact that individuals at genetic risk for psychosis are more prone to start using cannabis (ie, the association is due to rGE). In line with this, Ferdinand et al[27] showed that prodromal psychotic symptoms in cannabis-naive children and adolescents (4–16 years) predicted later onset of cannabis use (after 14 years). Nevertheless, Arseneault et al[14] had already shown in the Dunedin birth cohort sample that even after controlling for those children, who at age 11 years had reported psychotic-like experiences, the risk of developing schizophreniform psychosis at age 26 years in the cannabis users remained significantly increased. Furthermore, Henquet et al,[18] in a German cohort study including adolescents and young adults, found no statistically significant association between baseline subclinical psychotic symptoms and cannabis use at 3–5 years later. In the Christchurch Health and Development Study, a birth cohort study of 1055 children, data on cannabis use and psychotic symptoms were collected at ages 18, 21, and 25 years.[28,29] Analysis of the temporal association between frequency of cannabis use and psychotic symptoms showed that cannabis use had a positive and significant effect on psychotic symptoms, implying that increasing cannabis use was associated with increasing symptom levels. The effect of psychotic symptoms on cannabis use, however, was negative and appeared to have inhibited rather than increased cannabis use. Recently, Veling et al[30] used a case-control design, including first-episode schizophrenia patients and unaffected siblings of cases and controls, to investigate the extent to which rGE contributes to the association between cannabis (5 times or more lifetime) and psychosis. In this study, cannabis use was associated with schizophrenia, but there was no evidence for rGE because siblings of cases (at increased genetic risk) and controls did not differ in their lifetime cannabis consumption.

In order to investigate the association between psychosis proneness and cannabis use, Barkus and Lewis[31] investigated university students using the Schizotypal Personality Questionnaire (SPQ[32]). Although they found no association between schizotypy scores and frequency of cannabis use or age of first use, there was an association between having used cannabis at least once and higher scores on the disorganized dimension from the SPQ. Schiffman et al[33] further investigated the temporal association between disorganized symptoms measured with the SPQ and cannabis use. To assess the onset of schizotypal symptoms, the SPQ was modified by adding a follow-up question after each item, assessing when this experience was first noticed. Among recent users, the average age of onset of SPQ symptoms preceded age of first use of cannabis.[33]

To summarize mechanisms of rGE are very unlikely to explain the association between cannabis and psychosis because there is only modest evidence that genetic predisposition for psychosis predicts future cannabis use. In addition, most of the aforementioned longitudinal studies excluded individuals with psychotic symptoms at baseline and nonetheless found an effect of baseline cannabis on psychosis outcome at follow-up.[4,17] Other studies used the method of statistical adjustment and found that the effect of cannabis on psychosis remained significant after controlling for preexisting psychotic symptoms.[18,19,28] This suggests that the use of cannabis is causally related with psychosis, whereby cannabis is associated with a 2-fold increase in risk of developing psychotic illness, independently of preexisting psychosis liability.[14–16]

Differential Sensitivity to Delta-9-Tetrahydrocannabinol

Although there is good evidence that the use of cannabis is an independent risk factor for psychosis, fact remains that the vast majority of cannabis users never develop any psychotic symptoms and that only a minority experiences deleterious effects of delta-9-tetrahydrocannabinol (THC). It thus seems plausible to suggest that some individuals may be more sensitive to the psychotogenic effects of THC than others.

Experimental Studies

Experimental studies investigating the acute effect of cannabis showed that cannabis can induce transient psychotic symptoms as well as a wide variety of cognitive effects. In 1845, Moreau[34] described the effects of high doses of cannabis as "acute psychotic reactions." Much later, experimental studies on healthy individuals also showed that cannabis can induce dose-related transient psychotic symptoms in healthy individuals[35,36] and worsen symptoms in those with established psychosis illness.[2,37,38] Later studies on the acute effects of cannabis, furthermore, showed that there are great individual differences in how people respond to cannabis.[39,40]

In a paradigm designed to investigate the specific nature of this differential sensitivity, D'Souza et al[41] exposed healthy controls and patients with schizophrenia to THC, the main active ingredient in cannabis, given through the intravenous route. They found that THC significantly increased both positive psychotic and negative symptoms as assessed by the Positive and Negative Syndrome Scale. In addition, the patient group showed increased vulnerability to develop psychotic symptoms after THC. This is perhaps not surprising because by virtue of their patient status they obviously had a vulnerability to psychosis. However, they also showed abnormal sensitivity to the cognitive effects of THC. This finding is intriguing because impairments of memory, attention, and executive function are fundamental features in psychosis. Mild cognitive impairments have also been described in first-degree nonpsychotic relatives of patients with schizophrenia and are considered to define an endophenotypic expression of schizophrenia risk genes.[42,43] However, the evidence that psychotic patients show increased sensitivity to cannabis does not explain whether the sensitivity is an innate characteristic of the individual or whether it developed as part of the onset of psychosis.

Psychosis Liability

A first clue to the possibility of preexisting factors playing a role in this increased sensitivity to cannabis came from the apparent inconsistency that, on the one hand, psychosis liability is associated with a greater risk of starting to use cannabis,[27] while, on the other hand, statistical adjustment for psychosis liability did not reduce the association between cannabis use and later psychotic symptoms significantly.[19] Instead of adjusting for psychosis liability, several researchers then used a model of interaction in which psychosis liability, as measured psychometrically by questionnaire, was studied for its potential synergistic effects on the psychosis-inducing effects of cannabis. Henquet et al[18] investigated this in adolescents and young adults with high vs average liability for psychosis. Psychosis liability in this study was assessed by means of the Symptom Checklist (SCL-90-R[44]), a self-report questionnaire. The effect of baseline cannabis use (5 times or more) on the psychosis outcome after 3.5 years was much stronger in those with high liability for psychosis at baseline (23.8%) than in those with average liability (5.6%). Barkus and Lewis[31] investigated psychometric psychosis proneness and acute reactions to cannabis use (at least once) in university students by means of the Cannabis Experiences Questionnaire (CEQ) and the SPQ. The CEQ consists of 2 subscales measuring acute effects (the "pleasurable experiences" and "psychosis-like experiences" subscales) and "after-effects". High psychosis proneness scores in Barkus' study were associated with higher levels of pleasurable experiences, psychosis-like experiences, and cannabis after-effects.

Epidemiological studies, however, may not be sufficient to understand how exactly psychosis liability and cannabis interact to moderate the way an individual perceives and responds to his or her environment. Verdoux et al[45] therefore applied a momentary assessment technique (the experience sampling method [ESM] to investigate the acute effects of cannabis in the flow of daily life). ESM is a structured diary method in which subjects receive a digital wristwatch and a paper and pen ESM booklet.[46,47] Several times a day for 6 consecutive days, the watch emits a signal at random moments after which subjects are asked to complete a self-assessment form, collecting reports on affect and intensity of symptoms. In this study, the use of cannabis in between beeps was assessed as well. ESM allows the study of fluctuations in cannabis use, mood, and psychotic symptoms as they occur in the flow of daily life, thus taking into account variations between individuals with regard to the occurrence of symptoms and use of cannabis. Using this method, Verdoux et al[45] compared cannabis effects between students with high and average psychosis proneness (defined by the Community Assessment of Psychic Experiences [CAPE] questionnaire[48] and the MINI-International Neuropsychiatric Interview criteria for possible psychotic condition among subjects from the general population) and found that in daily life the acute effects of cannabis are moderated by an individual's level of psychometric psychosis liability. Those with high psychosis vulnerability reported more intense increases in psychosis-like symptoms. Individuals with low CAPE scores, on the other hand, were more likely to interpret the social context as friendly when under the influence of cannabis.[45]

Gene-Environment Interaction

Does Familial Liability Underlie the Differential Sensitivity for THC?

In order to test whether familial liability for psychosis might underlie the increased sensitivity to cannabis, McGuire et al[49] investigated family history of schizophrenia in a case-only design comparing cannabis users (evidenced by urinary screening) vs noncannabis users. In the case of massive environmentally mediated risk effects, heritability is hypothesized to go down, whereas in the case of GEI, heritability is expected to go up in the context of environmental risk.[50] In accordance with the GEI hypothesis, in which an individual's genotype moderates his or her response to cannabis, McGuire et al[49] found that individuals who developed acute psychosis after cannabis use were more likely to have a positive family history of schizophrenia than patients who screened negatively on cannabis use. Another study using a similar design, however, found no association between cannabis use and a positive family history, though in this latter study the family history data were obtained from case records rather than from direct interview and therefore may have been less accurate.[51] Arendt et al[52] compared familial predisposition for psychiatric disorder in patients with schizophrenia who were treated for cannabis-induced psychosis and patients with schizophrenia without a history of cannabis-induced psychosis. In this study, it was found that the predisposition rates of psychiatric disorders from first-degree relatives of individuals treated for cannabis-induced psychosis were virtually identical to those of individuals treated for schizophrenia. Apart from indicating that cannabis-induced psychosis could be an early sign of schizophrenia rather than a distinct clinical entity,[53] these results in addition show that cannabis may predominantly cause psychotic symptoms in those who are predisposed for psychosis.[52]

Is Psychometric Psychosis Liability Genetic in Nature?

From the aforementioned studies, it is clear that psychometrically defined psychosis liability moderates both the acute and the long-term effects of cannabis. Whether psychometric psychosis liability reflects a familial or genetic liability, however, remains a matter of debate. Psychometric psychosis liability or schizotypy refers to the level of subclinical positive psychotic symptoms, which are not necessarily associated with a diagnosis of clinical psychotic disorder defined by *DSM-IV*.[18,54,55] Psychosis liability is generally assessed by means of self-report questionnaires (the CAPE,[48] the SCL-90-R,[44] and the SPQ[32]). Increased levels of psychometric psychosis liability have been described as an endophenotype for psychosis.[56]

The proposition that subclinical psychotic symptoms may have a genetic origin comes from studies showing that first-degree relatives of patients with schizophrenia display higher levels of subclinical symptoms than individuals from the general population.[57] In addition, there is research to show that in samples that were not selected specifically to investigate psychotic disorder, the positive dimensions of subclinical psychosis cluster in families.[58] These subclinical symptoms of psychosis have also been shown to be associated with subtle cognitive impairments that may be regarded as markers of familial transmission of liability to psychosis.[43] Twin studies have shown that genetic factors play a role in the manifestation of subclinical psychotic symptoms,[59,60] and by using genetic linkage data, Fanous et al[61] claimed that the genetic loci that have been found to be associated with schizophrenia may also affect schizotypal traits in nonpsychotic relatives. Thus, although environmental risk factors could explain part of the family-specific variation of positive psychosis dimensions, psychometric psychosis liability is likely to be genetic in nature as well. The exact underlying molecular mechanisms, however, have yet to be defined.

COMT Val158Met Genotype and Cannabis Use

A study by Caspi et al[62] was the first to show direct evidence of a GEI in the cannabis-psychosis relationship by looking at a functional polymorphism in the *catechol-O-methyltransferase (COMT)* gene. The *COMT* gene codes catechol-O-methyltransferase (COMT) that is an enzymatic inactivator of dopamine, norepinephrine, and epinephrine. In the prefrontal cortex, COMT is critical in the breakdown of dopamine. The *COMT* gene contains a functional polymorphism, involving a *Met* to *Val* substitution at codon 158, which results in 2 common allelic variants, the *valine* (Val) and the *methionine* (Met) allele, associated with high vs low enzyme activity,[63,64] respectively. Increased COMT activity associated with the *Val* allele may result in a combination of (1) reduced dopamine neurotransmission in the prefrontal cortex, which is associated with impairments in working memory, attention, and executive functioning[65,66] and subsequently (2) increased levels of mesolimbic (phasic) dopamine signaling,[67] which is hypothesized to result in an increased risk of experiencing delusions and hallucinations.[68] Systematic reviews investigating *COMT Val158Met* genotype in relation to the broader psychosis phenotype, however, have shown no evidence of an association between *COMT Val158Met* genotype and schizophrenia or between *COMT Val158Met* genotype and familial liability to psychosis.[69,70] Caspi et al,[62] however, found that *COMT* moderated the risk of developing adult (at age 26 years) schizophreniform disorder following cannabis use during adolescence. For individuals homozygous for the *COMT Val158Met Val* allele, the relative risk of developing psychotic illness after adolescent cannabis exposure was 10.9, whereas in individuals homozygous for the *Met* allele, the risk was only 1.1 (figure 1). In this study, there was no evidence for rGE because subjects of the *Val/Val* genotype were not more prone to start using cannabis at an earlier age or to use cannabis more frequently than carriers of the *Met* allele.[62]

In an effort to further understand the interaction between cannabis and *COMT Val158Met* genotype in relation to the cognitive endophenotype for psychosis, Henquet et al[71] conducted a double-blind, placebo-controlled study of THC exposure in patients with psychotic illness and healthy controls (figure 2). THC acutely impaired memory function and attention, and in line with Caspi's finding, individuals with the *Val/Val* genotype were most sensitive to these cognitive effects of THC. Again, in this study, there was no evidence for rGE because *COMT Val158Met* genotype on its own was neither associated with cognitive impairments nor associated with frequency of cannabis use or being a patient.[71] In the only other reported study to address this question, Zammit et al[72] used a case-only design but found no association between *COMT Val158-Met* genotype and cannabis use (based on interview and case note records) in schizophrenia patients in study nor with other single-nucleotide polymorphisms (SNPs) within the *COMT* gene, however, the quality of the data on cannabis use in this study was limited.

Cannabinoid Receptor gene and the Genes It Might Interact With

Again, in an attempt to further investigate the molecular basis of increased sensitivity to THC in relation to psychosis outcome, Zammit et al[72] examined variations within the *cannabinoid receptor (CNR1)* gene in the same sample of patients with schizophrenia, as well as in healthy controls. The *CNR1* gene codes for the CB1 receptors and is located at 6q14–q15, a schizophrenia susceptibility locus.[73] An association between schizophrenia and a polymorphism nearby the *CNR1* gene (*AAT repeats in the 3' flanking region*) has been reported before.[74] Zammit, however, found no association between schizophrenia and another polymorphism in the *CNR1* gene (*rs1049353*). To further investigate variations within the *CNR1* gene in interaction with cannabis exposure, Zammit et al used a case-only design but found no *rs1049353* genotype differences between patients. The *CNR1* gene is of interest because it has been suggested

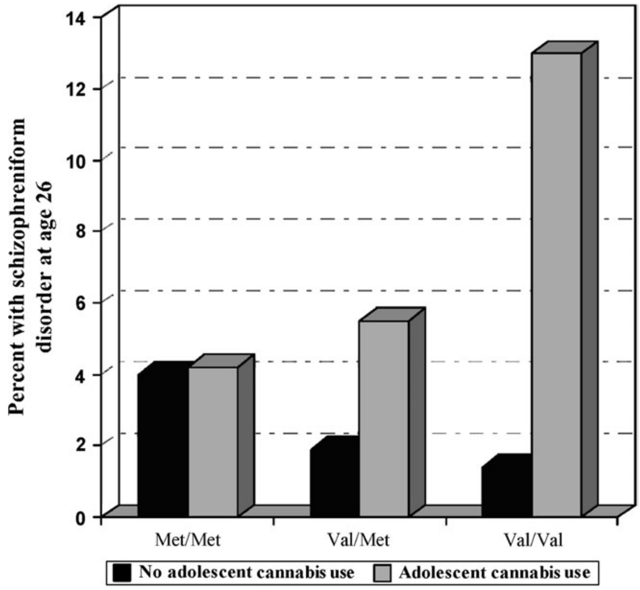

Fig. 1. Cannabis Use During Adolescence Significantly Increased the Risk of Developing a Schizophreniform Disorder at Age 26 y but Only in Those Individuals Who Carried 1 or 2 *COMT Val158Met Val* Alleles. Ref. 62

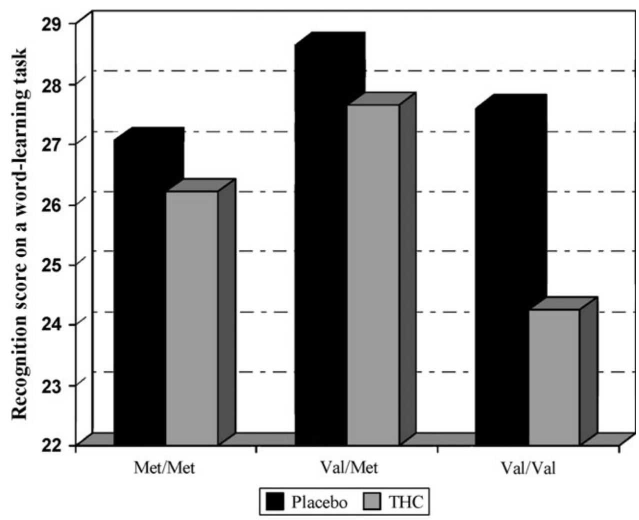

Fig. 2. The Val158Met Functional Polymorphism of the *Catechol-O-Methyltransferase (COMT)* Gene Moderated Sensitivity to the Cognitive Effects of Delta-9-Tetrahydrocannabinol (THC). THC significantly decreased memory performance; however, subjects with the *Val/Val* genotype were significantly more impaired on a delayed recognition task after THC than those with the *Met/Met* or the *Val/Met* genotype. Ref. 71.

to modulate striatal dopamine,[75] and in a recent functional magnetic resonance imaging study it was found that 4 SNPs in the *CNR1* gene moderate striatal response to emotional rewarding stimuli.[76] Other genes involved in regulation of dopamine in the mesolimbic system may be of interest as well, in particular because a recent positron emission tomography study showed that variations in both the *COMT* and the *dopamine transporter (DAT)* gene moderated smoking-induced dopamine release.[77] Finally, a study investigating GEI between the *neuregulin 1 (Nrg1)* gene and THC exposure showed that heterozygous *Nrg1* transmembrane domain knockout mice (*Nrg1 HET*) were more sensitive to the acute effects of THC on several behavioral outcome measures.[78] This suggests that variation in the *Nrg1* gene may play a role in the sensitivity for THC as well. In this study, THC exposure also increased prepulse inhibition (a paradigm for study of sensorimotor gating, which is known to be impaired in schizophrenia) but only in *Nrg1 HET* mice.

Furthermore, recent evidence has raised the question of abnormal interaction between the γ-aminobutyric acid (GABA)–mediated neurons and endocannabinoid systems in schizophrenia. Eggan et al[79] reported that CB1 receptor messenger RNA and protein levels are decreased in the dorso-lateral-prefrontal cortex of subjects with schizophrenia; these changes appeared to be associated with deficient GABA synthesis in cholecystokinin (CCK) basket neurons. It has been shown that the activation of CB1 receptors reduces GABA release from the axon terminals of CCK basket neurons.[80] Therefore, downregulation of CB1 receptors might be a compensatory mechanism attempting to reduce the suppression of inhibition mediated by endogenous cannabinoids. These findings suggest that the list of genes to investigate as possibly interacting with exposure to cannabis use in increasing the risk of psychosis should be broadened to include those regulating the GABA system.

Genes Off or On: Epigenetic Mechanisms

Repeated exposure to drugs may elicit permanent changes in gene expression patterns via epigenetic mechanisms.[81] Several studies have explored the effect of THC on patterns of gene expression in the central nervous system.[82,83] A number of transcripts show up- or downregulation, which demonstrates that the effects of THC extend into the nucleus, well beyond cell surface receptor proteins. As yet, no overall pattern of intracellular effects can be discerned because tissue samples have included a mixture of different cell types, both neuronal and glial. Approaches based on whole-cell patch clamp and reverse polymerase chain reaction may be more fruitful in deciphering the effects of THC on gene transcription in specific neuronal cell types.[84] A major challenge is elucidation of the intracellular underpinnings of prolonged alterations in the electrical phenotype of specific cells and local circuitry. Recent work has demonstrated that the impact of THC on interneuronal signaling can persist for days to weeks following the period of receptor stimulation. For example, Hoffman et al[85] showed that following repeated exposure to THC, hippocampal long-term potentiation was impaired for 14 days. Similarly, a single exposure to THC was shown to elicit a 3-day impairment in long-term depression (LTD) at cortico-accumbens synapses.[86] Interestingly, following chronic THC, cortico-accumbens LTD showed recovery, which was mediated via upregulation of presynaptic type II metabotropic glutamate receptors.[87] The epidemiological evidence indicates that there can be a considerable delay (months to years) between the use of cannabis and the onset of schizophrenia. An important question is whether THC elicits maintained transcriptional changes in neural cells, which persist long after drug use has ceased. Specifically, does THC impact on the regulation of histone proteins and DNA methylation in key neuronal subtypes? Developments in chromatin immunoprecipitation assays now permit exploration of such questions.[88]

Beyond GEI

Gene × Gene × THC Interaction

It is unlikely that variation in a single gene accounts for the differential sensitivity to THC in individuals at risk for psychosis. Evidence that *COMT Val158Met* genotype and schizotypy are associated remains inconclusive,[89,90] which suggests that *COMT Val158Met* genotype and psychometric psychosis liability may not reflect one and the same mechanism. More likely, the molecular basis of psychometric psychosis liability may be related to other genes as well. Indeed, Henquet et al[71] showed in the aforementioned experimental study that *COMT Val158-Met* genotype and psychometric psychosis liability interact with each other to moderate THC effects on transient psychotic symptoms. Thus, carriers of the *Val* allele were more sensitive to the psychotogenic effects of THC, but this was conditional on prior level of psychometric psychosis liability. The same finding was observed in an ESM study investigating acute effects of cannabis on psychotic symptoms in daily life in patients with psychosis and healthy controls. In this study as well, cannabis significantly increased hallucinatory experiences ("hearing voices") but only in those individuals who (1) were carriers of the *COMT Val158Met Val* allele and (2) also had high levels of psychometric psychosis liability.[91] Although this 3-way interaction needs replication, it suggests that gene-gene interactions may underlie the association between cannabis and psychosis. This also provides an explanation for the observation from epidemiological work that only a minority of those exposed to cannabis develop schizophrenia. Interaction between genes has been described in schizophrenia research before. For example, a polymorphism in the *dopamine*

D2 receptor gene was found to interact with the *Val158-Met* functional polymorphism in the *COMT* gene on working memory performance, a putative cognitive endophenotype for psychosis.[92] Gene-gene interaction associated with striatal dopamine response was reported as well between a repeat polymorphism in the *DAT* gene and the *COMT Val158Met* polymorphism.[93]

Cross-sensitization Between Stress and THC

In addition to genetic moderation, environmental factors, however, may interact with each other as well on psychosis risk. A first clue for this with respect to cannabis comes from a study by Houston et al,[94] in which childhood trauma was investigated in association with psychosis. Childhood maltreatment is reported more frequently by patients with psychosis than controls.[95] There is evidence of an association between severe stress early in life and the development of later psychotic symptoms; however, whether childhood trauma is an independent and causal factor for psychosis remains a matter of debate.[96] Interestingly, Houston found a significant interaction between early exposure to cannabis (at least once before the age of 16 years) and childhood sexual trauma on psychosis outcome. Sexual trauma significantly increased the risk to develop a diagnosis of psychosis but only in those individuals who had used cannabis before the age of 16 years. No main effect of cannabis use or sexual trauma on psychosis outcome was observed[94] (figure 3). It has been suggested that psychotic reactivity to stress results from a sensitization process through which previous exposure to stress sensitizes people to stresses of daily life[97]. Sensitization refers to the observation that individuals who are exposed repeatedly to an environmental risk factor may develop progressively greater responses over time finally resulting in a lasting change in response amplitude.[98] Exposure to THC increases the risk for psychosis in a dose-response fashion,[18] which might be suggestive of a sensitization process as well. The finding by Houston suggests that the additive effect of early childhood trauma and cannabis on psychosis risk may result from a cross-sensitization process between repeated exposure to stress and THC. Cougnard et al[99] described similar additive effects of developmental risk factors (cannabis use, childhood trauma, and urbanicity) on psychosis persistence. Surprisingly, few studies have investigated possible cross-sensitization between stress and THC. Studies in rodents showed that THC-induced increase in dopamine uptake was higher under stressful conditions than under normal conditions,[100,101] and pretreatment with THC altered the dopaminergic response to stress in rats. This is interesting because acutely psychotic patients show excessive dopaminergic response to amphetamine, and the degree of response is related to the intensity of psychotic symptoms.[102,103] Recently, Booij et al[104] provided first insights into cross-sensitization processes between stress and psychostimulants in humans by showing that stress-induced dopamine increase was significantly higher among individuals who were repeatedly treated with amphetamine than when these individuals were amphetamine naive.

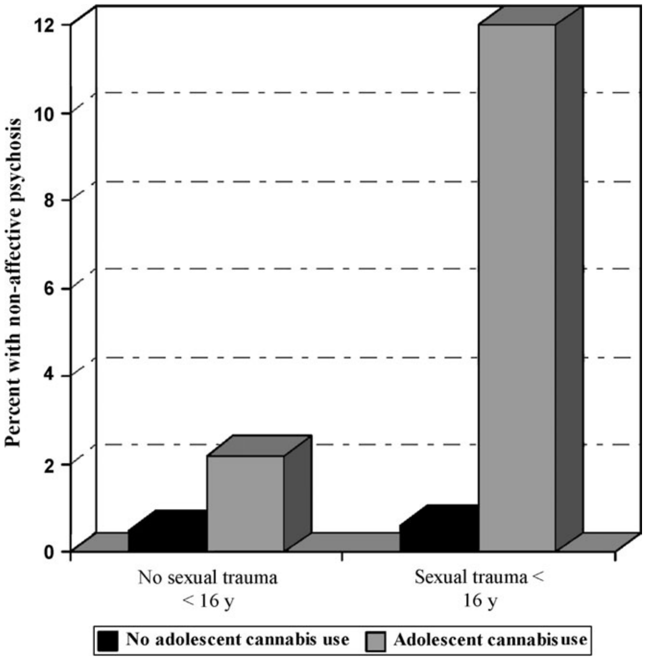

Fig. 3. Cannabis Use During Adolescence Significantly Increased the Risk of Developing Nonaffective Psychosis Later in Life but Only in Those Individuals Who Experienced Sexual Trauma During Childhood. Ref. 94.

Conclusion

Only a small proportion of those who use cannabis develop psychosis, but for these unfortunate individuals, cannabis appears to have a dramatically detrimental impact on their mental health. Genetic as well as environmental factors have been shown to underlie this differential sensitivity to cannabis and its active ingredient THC. In this interplay between genes and the environment, it is unlikely that mechanisms of rGE explain the cannabis-psychosis link. GEIs, however, are more likely to underlie the complex interactions between cannabis and psychosis, whereby multiple variations within multiple genes—rather than one single genetic polymorphism—may set an individual's vulnerability at birth to develop later psychosis. Several environmental factors during the course of development, such as cannabis use and stress, may then impact on these vulnerabilities and reinforce a shift forward on the psychosis continuum toward a lower threshold to experience psychotic symptoms and to ultimately develop clinical psychotic disorder. Intrinsic to the concept of a continuum is changeability of an individual's position on the psychosis continuum over time. In this frame, psychological and pharmacological treatment will limit further dysregulation and sensitization processes, whereas persistent cannabis use may continue to put an individual at risk of dysregulation of, eg, the dopamine system and subsequent chronic states of psychotic illness. Further experimental work on the biological mechanisms underlying these GEIs is therefore urgently needed to better understand the pathway by which THC may cause psychosis in the short and long term.

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